

## Effects of cholinesterase inhibitors

If acetylcholine was released at locations where it acted on sympathetic nerve terminals, then drugs that affected cholinergic mechanisms should have secondary effects arising from the way in which actions of the acetylcholine on sympathetic noradrenergic transmission were affected. A number of observations designed to investigate the cholinergic link hypothesis of Burn & Rand (see Introduction for references) has been carried out. Only those in which anticholinesterase drugs were used will be reviewed briefly here. The expectation of the cholinergic link hypothesis is that anticholinesterases might enhance noradrenergic transmission. In the light of other knowledge, there is the possibility that there would be inhibition of noradrenergic transmission mediated by acetylcholine acting on prejunctional cholinceptors. In most of the experiments concerned with the cholinergic link hypothesis, atropine was used to block the postjunctional action of acetylcholine. However, potentiation of the action of acetylcholine by inhibiting enzymatic hydrolysis might overcome blockade of muscarinic cholinceptors thereby confounding the findings of such experiments.

Inhibitors of cholinesterase enhanced responses to sympathetic nerve stimulation in rabbit uterus (Varagic, 1956) and isolated heart (Hukovic, 1966), guinea-pig vas deferens (Boyd, Chang & Rand, 1960; Burn & Weetman, 1963) and taenia coli (Ng, 1966), dog femoral artery *in situ* (Bernard & de Schaepdryver, 1964) and retractor penis (Armitage & Burn, 1967), perfused rabbit ear (Burn & Rand, 1960a) and rabbit ear artery (Rand & Varma, 1970) and rat mesenteric vessels (Malik, 1970). However, the enhancing effect reported on the cat nictitating membrane by Bacq & Frederiq (1935) and by Burn, Rand & Wein (1963) could not be repeated by Mirkin & Cervoni (1962), Gardiner, Hellmann & Thompson (1962) or Bowman, Callingham & Cuthbert (1964), but see Burn & Rand (1965). Furthermore, no enhancing effect could be detected in cat spleen (Blakeley *et al.*, 1963; Thoenen, *et al.*, 1966), rabbit ear artery (Hume *et al.*, 1972) and rabbit pulmonary artery (Bevan & Su, 1964). To complicate matters further, responses to sympathetic nerve stimulation were reduced by cholinesterase inhibitors in cat pilomotor muscles (Hellmann, 1963), dog gastric artery (Van Hee & Vanhoutte, 1978) and retractor penis muscles of various species (Klinge & Sjöstrand, 1977).

### Effect of acetylcholine released from parasympathetic nerves on noradrenergic transmission

The tissues with a double supply comprising cholinergic parasympathetic and noradrenergic sympathetic inputs include the heart, the iris, the salivary glands, the gastrointestinal tract and pelvic viscera. Of these, the heart is perhaps the most easily studied: in any event, it has been the most studied.

Acetylcholine released by vagus nerve stimulation in the isolated perfused rabbit heart inhibited the release of noradrenaline in response to sympathetic nerve stimulation in the rabbit isolated heart (Löffelholz & Muscholl, 1970; Langley & Gardiner, 1977; Muscholl *et al.*, 1979), but not in the isolated perfused chicken heart (Löffelholz, 1975).

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In field stimulated atria, both acetylcholine and noradrenaline would be released, and in rabbit atria, the released acetylcholine inhibited noradrenaline release since atropine increased, and physostigmine decreased the stimulation-induced release of noradrenaline and the positive inotropic response (Hope et al., 1974; Muscholl & Muth, 1982). Similarly, in dog papillary muscle, the positive inotropic response to sympathetic nerve stimulation was enhanced by atropine (Endoh & Hashimoto, 1970). However, these effects were not demonstrable in guinea-pig atria, on which exogenous acetylcholine had no effect (Hope et al., 1974; Story et al., 1975), or in rat atria, in which exogenous acetylcholine did inhibit noradrenaline release (Loiacono & Story, unpublished observations).

Observations on the dog heart *in situ* have demonstrated the importance of cholinergic modulation of cardiac sympathetic tone by inhibition of noradrenaline release in addition to the direct actions of acetylcholine on the pacemaker cells and the contractile activity of cardiac myocytes. Levy & Blattberg (1976) and Lavallée et al. (1978) showed that stimulation of the vagus nerves decreased the release of noradrenaline as well as the positive inotropic response to sympathetic nerve stimulation in the dog heart.

The complex interaction between the cholinergic and noradrenergic mechanisms in the control of cardiac activity was first noted by Rosenblueth & Simeone (1934), when they observed that the extent of the bradycardia produced by vagal stimulation was greater in the presence than in the absence of sympathetically maintained tachycardia. Similar observations were made by other workers (Samaan, 1935; Levy & Zieske, 1969; Warner & Russell, 1969). If the parameters of stimulation of the vagus and sympathetic nerves to the dog heart are adjusted so that the responses to each separately are equal in magnitude but opposite in direction, then when the two nerves are stimulated simultaneously the heart rate decreases as if there were no sympathetic stimulation (Levy & Zieske, 1969). This effect has been termed 'accentuated antagonism' (Levy, 1971; Levy & Martin, 1979; Stuesse, Wallich & Levy, 1979), signifying that the resultant effect is not merely the algebraic sum of the two separate responses of bradycardia and tachycardia to vagal and accelerans nerve stimulation, respectively; in fact, the bradycardia predominates (Levy, 1984). This phenomenon also occurs when the pacemaker is in the atrioventricular bundle rather than in the sinoatrial node (Wallick, Felder & Levy, 1978). In contrast, the effects of vagal and sympathetic nerve stimulation on atrioventricular conduction time are simply additive (Levy & Zieske, 1969; Wallick, Felder & Levy, 1982).

The increase in heart rate produced in the conscious dog by methylatropine (a quaternary analogue of atropine that does not enter into the brain) is due to blockade of the inhibitory effect of acetylcholine released by tonic activity of the vagus nerves on prejunctional muscarinic cholinergic receptors of noradrenergic terminals, resulting in a greater release of noradrenaline from the tonically active sympathetic nerves (Lokhandwala, Cavero & Buckley, 1973).

The effects on myocardial contractility of cholinergic and noradrenergic mechanisms, like those on chronotropic activity,

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display a complex interaction. The effect of acetylcholine on ventricular contractility in the dog is a small reduction; however, when the sympathetic nerves are stimulated or a noradrenaline infusion is given, the negative inotropic effect of acetylcholine is much greater (Hollenberg, Carriere & Barger, 1965). Similar observations on the negative inotropic responses to vagal stimulation were made by Levy, Ng, Martin & Zieske (1966): in their studies, vagal stimulation alone was virtually without effect on ventricular contractility; however, when the force of contraction was increased by sympathetic nerve stimulation, vagal stimulation decreased the force almost to the prestimulation level. The effects of vagal and sympathetic stimulation on the force of atrial contractions exhibited similar interactions (Stuesse et al., 1979).

The evidence indicates clearly that the interaction between the cholinergic and noradrenergic innervations of the heart are not confined to their opposing postjunctional actions but extend to prejunctional interactions (Levy, 1971, 1984; Higgins, Vatner & Braunwald, 1973; Story et al., 1975). The postjunctional interactions have been described by Watanabe, Lindemann & Fleming, (1984).

In addition to cholinergically induced inhibition of noradrenergic transmission, the reverse interaction, noradrenergically induced inhibition of cholinergic transmission has been reported (Vizi & Knoll, 1971; Story et al., 1975; see also: Wetzel, Goldstein & Brown, 1985; Loiacono & Story, 1986). Neuronal interactions may also involve peptide cotransmitters in addition to the classical transmitters of autonomic nerves. Thus, Potter (1985, 1987) showed that stimulation of cardiac sympathetic nerves in the dog resulted in a prolonged inhibition of the response to vagus nerve stimulation that was not due to noradrenaline but was mimicked by neuropeptide Y. It remains to be shown whether there is a peptide cotransmitter in cardiac cholinergic nerves and, if so, whether it affects noradrenergic transmission.

#### Effects of acetylcholine released from sympathetic cholinergic nerves on noradrenergic transmission

The two tissues to be considered in this section are the vas deferens and blood vessels. They are generally thought to be innervated by sympathetic nerves, except for some blood vessels in certain specialised regions such as the blush areas and erectile tissue which also receive a parasympathetic innervation. Nevertheless, they have a cholinergic as well as a noradrenergic innervation. In the case of the vas deferens it is not clear whether there are separate cholinergic nerves or whether the noradrenergic nerves contain a cholinergic component.

#### Vas deferens

Prejunctional muscarinic cholinceptors may be involved in the neuronal control of the activity of the guinea-pig vas deferens, in which muscarinic agonists inhibit stimulation-induced noradrenaline release (Stjärne, 1975; Leighton & Westfall, 1976). There appear to be cholinergic nerves in this tissue since it contains acetyltransferase (Ohlin & Strömblad, 1963) and field stimulation releases acetylcholine (Knoll, Somogyi, Illes & Vizi, 1972).

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If endogenously released acetylcholine had an inhibitory effect on stimulation-induced noradrenaline release, blockade of the prejunctional muscarinic cholinergic receptors should enhance noradrenaline release. This does not appear to be the case in most tissues (see Starke, 1977). However, there are exceptions, as mentioned above for rabbit atria, and here for the vas deferens.

The endogenously released acetylcholine apparently inhibits noradrenaline release since the amount of noradrenaline released by field stimulation is increased by atropine (Stjärne, 1975). Paradoxically, muscarinic agonists enhance the contractile response to field stimulation (Sjöstrand, 1961; Sjöstrand & Swedin, 1968; Lambie & Lambie, 1975), but this is presumably by a postjunctional action: whether it involves interaction with the contractile effect of noradrenaline or of the non-noradrenergic motor transmitter (ATP), or both, has not been determined.

### Blood vessels

The physiological significance of the inhibition by acetylcholine of noradrenergic transmission to blood vessels is uncertain. The vasodilator action of acetylcholine is mediated by the release of an endothelium-derived relaxing factor (EDRF) (Furchgott & Zawadski, 1980; Furchgott, 1983). However, the inhibitory effect of acetylcholine on noradrenergic transmission is not affected by removal of the endothelium, and therefore does not involve EDRF (Loiacono & Story, 1984). In some blood vessels, EDRF is not involved in the vasodilator response to acetylcholine (Brayden & Large, 1986).

Where there is a cholinergic innervation, as is the case for blood vessels of skeletal muscle (Burn, 1938; Uvnas, 1960, 1967), the vasodilator responses elicited by stimulation of these nerves could be due to inhibition of a noradrenergically maintained vasoconstrictor tone, as suggested by Vanhoutte & Shepherd (1973). However, there is little or no evidence for the existence of a cholinergic innervation in most of the blood vessels in which the inhibitory effect of acetylcholine on noradrenergic transmission has been demonstrated. There is some evidence for a cholinergic innervation of the blood vessels in the rabbit ear (Armin, Grant, Thompson & Tickner, 1953; Holton & Rand, 1962), and cholinesterases are associated with the periarterial sympathetic nerve fibres of the artery (Waterson *et al.*, 1970). However, according to Hume & Waterson (1978), there are no cholinergic nerves associated with the rabbit ear artery. Atropine has only slight effects on the vasoconstrictor responses to sympathetic nerve stimulation in the rabbit ear (Holton & Rand, 1962) or the isolated artery (Rand & Varma, 1970), whereas blockade of an inhibitory component due to simultaneous release of acetylcholine would be expected to result in a greater vasoconstrictor response.

Blood vessels with a cholinergic innervation in which endogenously released acetylcholine has been shown to inhibit noradrenaline release include the canine coronary artery (Cohen, Shepherd & Vanhoutte, 1984) and gastric artery (Van Hee & Vanhoutte, 1978). Similar findings have been obtained in the perfused vasculature of the rabbit lung (Mathé *et al.* 1977).

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## Conclusion

There is overwhelming evidence for the presence of cholinceptors on sympathetic noradrenergic nerve terminals and their distribution appears to be ubiquitous in terms of mammalian species and tissues innervated.

Activation of prejunctinal nicotinic cholinceptors results in release of noradrenaline and sometimes in facilitation of stimulation-induced noradrenaline release. Their physiological role is uncertain and the only attempt to assign them a role in the cholinergic link hypothesis of noradrenergic transmission has faded from prominence.

Activation of prejunctinal muscarinic cholinceptors results in inhibition of noradrenaline release and they appear to be involved in the physiological control of neurotransmission, at least in those tissues that contain a cholinergic as well as a noradrenergic innervation.

Other effects on noradrenergic transmission produced by cholinceptor agonists are of uncertain significance and remain as curiosities.

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Table 1. Early reports on the sympathomimetic action of acetylcholine in the presence of atropine and of other nicotinic agonists.

Cardiac preparations:

Burn & Dutta, 1948  
Heymans & Bennati, 1949  
Jacob, 1952  
Kottegoda, 1953a  
Szentiványi & Kövér, 1956  
Holtz & Westermann, 1955  
Burn & Rand, 1958a

Vascular preparations

Kottegoda, 1953b  
Burn & Rand, 1957, 1958b  
Burn, Leach, Rand & Thompson, 1959  
Steinsland & Furchgott, 1975a,b

Spleen

Chernigovskii, 1940  
Brandon & Rand, 1961  
Daly & Scott, 1961  
Macmillan & Rand, 1962  
Boatman & Brody, 1964

Respiratory tract

Hawkins & Paton, 1958

Intestinal preparations

Ambache & Edwards, 1951  
Gillespie & MacKenna, 1960, 1961.

Skin (piloerector muscles)

Brücke, 1935  
Coon & Rothman, 1940  
Burn et al., 1959  
Burn & Rand, 1960a

Nictitating membrane

Thompson, 1958  
Burn et al., 1959

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Table 2. Reports of release of noradrenaline or of radioactivity from (<sup>3</sup>H)-noradrenaline-labelled tissues by nicotinic agonists. See text for further references.

Cardiac preparations

Rabbit

Richardson & Woods, 1959  
 Lindmar & Muscholl, 1961  
 Lindmar, 1962  
 Muscholl & Maître, 1963  
 Lindmar et al., 1967, 1968  
 Löffelholz, 1967, 1970a,b  
 Löffelholz & Muscholl, 1969  
 Fozard & Muscholl, 1972  
 Muscholl, 1973b  
 Göthert, 1974  
 Starke & Montel, 1974  
 Dubey, Muscholl & Pfeiffer, 1975  
 Göthert, Kennerknecht & Thielecke, 1976  
 Sarantos-Laska, Majewski, McCulloch & Rand, 1980a

Guinea-pig

Bhagat, Robinson & West, 1967  
 Lindmar et al., 1968  
 Westfall, 1971a  
 Westfall & Brasted, 1972, 1973, 1974  
 Allen, Glover, Rand & Story, 1972b  
 Sorimachi, Oesch & Thoenen, 1973  
 Westfall & Hunter, 1974.

Rat

Sharma & Banerjee, 1978  
 Fuder, Siebenborn & Muscholl, 1982b  
 (but see Westfall & Saunders, 1977)

Spleen (cat)

Brandon & Boyd, 1961  
 Blakeley, Brown & Ferry, 1963  
 Herrting & Widholm, 1965  
 Fischer, Weise & Kopin, 1966  
 Davey, Haydon & Scholfield, 1968  
 Krauss, Carpenter & Kopin, 1970  
 Kirpekar, Prat, Puig & Wakade, 1972

Vascular preparations (rabbit)

Aorta

Kiran & Khairallah, 1969

Pulmonary artery

Su & Bevan, 1970  
 Nedergaard & Schrold, 1973, 1977  
 Starke & Weitzell, 1978

Ear artery

Allen, Glover, McCulloch, Rand & Story, 1975

Intestinal tissue

Rabbit colon

Gillespie & MacKenna, 1960

Guinea-pig taenia caeci

Kuchii, Miyahara & Shibata, 1973

Vas deferens (rat)

Jayasundar & Vohra, 1978

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Table 3. Evidence for a cholinergic component in the predominantly noradrenergic sympathetic nerve supply. See text for further references.

Cat

Nictitating membrane

Bacq & Fredericq, 1935  
Burn & Rand, 1960a  
Nystrom, 1962

Heart

Folkow, Frost, Halger & Uvnas, 1948  
Day & Rand, 1961

Spleen

Burn & Rand, 1960a  
Brandon & Rand, 1961

Uterus

Sherif, 1935  
Burn & Rand, 1960a

Hind leg

Folkow et al., 1948

Dog

Hind leg

Bülbring & Burn, 1935  
Bogaert, De Schaepdryver & De Vleeschhouwer, 1961  
McCubbin, Kaneko & Page, 1961

Tongue

von Euler & Gaddum, 1931

Rabbit

Intestine

Gillespie & MacKenna, 1959  
Day & Rand, 1961

Atria

Hukovic, 1959

Ear

Burn & Rand, 1960a  
Holton & Rand, 1962

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